Adult-onset deletion of Pten increases islet mass and beta cell proliferation in mice.

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Public Summary:
In this manuscript, we tested whether manipulating the beta cells growth signal (i.e. PTEN) is capable of reversing the aging of beta cells. Beta-cells located in the pancreas produces insulin and is critical for the maintaining blood levels of glucose in healthy individuals. Using mouse as a model, we have found that the size of the islets which are formed by beta-cells and their ability to produce insulin are dependent on PTEN. In this manuscript, we showed that removing the PTEN signal in adult beta-cells is also capable of affecting the size of islets and their production of insulin.

Scientific Abstract:
AIMS/HYPOTHESIS: Adult beta cells have a diminished ability to proliferate. Phosphatase and tensin homologue (PTEN) is a lipid phosphatase that antagonises the function of the mitogenic phosphatidylinositol 3-kinase (PI3K) pathway. The objective of this study was to understand the role of PTEN and PI3K signalling in the maintenance of beta cells postnatally. METHODS: We developed a Pten (lox/lox); Rosa26 (lacZ); RIP-CreER (+) model that permitted us to induce Pten deletion by treatment with tamoxifen in mature animals. We evaluated islet mass and function as well as beta cell proliferation in 3- and 12-month-old mice treated with tamoxifen (Pten deleted) vs mice treated with vehicle (Pten control). RESULTS: Deletion of Pten in juvenile (3-month-old) beta cells significantly induced their proliferation and increased islet mass. The expansion of islet mass occurred concomitantly with the enhanced ability of the Pten-deleted mice to maintain euglycaemia in response to streptozotocin treatment. In older mice (>12 months of age), deletion of Pten similarly increased islet mass and beta cell proliferation. This novel finding suggests that PTEN-regulated mechanisms may override the age-onset diminished ability of beta cells to respond to mitogenic stimulation. We also found that proteins regulating G1/S cell-cycle transition, such as cyclin D1, cyclin D2, p27 and p16, were altered when PTEN was lost, suggesting that they may play a role in PTEN/PI3K-regulated beta cell proliferation in adult tissue. CONCLUSIONS/INTERPRETATION: The signals regulated by the PTEN/PI3K pathway are important for postnatal maintenance of beta cells and regulation of their proliferation in adult tissues.

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